Practitioner's Docket No.: 868_012 ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Noriaki KATO, Hiroshi NAGANO, Kaori TANIKO and Takahito JOMORI

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For: PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY

DECLARATION UNDER 37 CFR ' 1.132

Sir:

I, Mara Lorenzi, a permanent resident of the United States of America, hereby declare and state:

1. I have a doctor of medicine degree conferred to me by the University of Turin Medical School in Italy in 1971. I have received the following licensures and certificates: Italian Licensure, ECFMC certificate, FLEX certificate, Specialization in Internal Medicine (Italy), California license registration (currently inactive), American Board of Clinical Pathology certificate, and Massachusetts License registration.

2. I have been employed by the Schepens Eye Research Institute, Harvard Medical School (20 Staniford St. Boston MA 02114) as Professor of Ophthalmology since 2004. I have had a total of 22 years of work and research experience in the areas of Diabetes and Ophthalmology. I had several major committee assignments at the University of California San Diego (UCSD) Medical School; Harvard Medical School; Dept. of Ophthalmology, Harvard Medical School; Harvard Affiliated Institution Schepens Eye Research Institute, UCSD Medical Center; and at NIH, JDRF, NIDDK Diabetic Complications Consortium.

3. I am a member of the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), American Association for the Advancement of Science, The Endocrine Society, American Federation for Medical Research, Massachusetts General Physicians Organization, Inc., and Societé Française de Microcirculation. I have been a member of several editorial boards, which were Diabetes, Nutrition and Metabolism (1987-1997), the

Editorial Advisory Council, Journal of Endocrinological Investigation(1990-1996), Diabetes Metabolism Reviews(1993-1998), Diabetes/Metabolism Research and Reviews(1998-2004), Journal of Clinical Investigation(1998), and Diabetologia (2003-2005). I have had many awards and honors which were Montecatini Prize for Therapy (Italy) for study of the mechanisms of action and clinical use of antiandrogens (Doctoral Thesis)(1972), Scholarship from the Department of Education, Italian Government, for specialization in Endocrinology(1973-1975), Endowed position of Institute Scientist, Schepens Eye Research Institute(1987- present), Mentor-Based Postdoctoral Fellowship Award of the American Diabetes Association(1992-1995), Mary Jane Kugel Award of the Juvenile Diabetes Foundation(1994, 2003, 2006), Honor Lecture, 16th Congress of the Italian Diabetes Association(1996), First recipient of the Alessandro Beretta-Anguissola Prize of the University of Rome "La Sapienza" for scientific merits in Internal Medicine(2003), Listed in Guide to America's Top Physicians –Consumers' Research Council of America (2004- present), and First recipient of the Golden Palm from civic organizations in Bordighera, Italy, for "honoring the hometown in the world"(2008) .

4. My publications, presentations, original articles, proceedings of meetings, reviews and book chapters, and abstracts, are as follows.

1) Regional, National, and International Presentations and Contributions

Honor, Plenary, and State-of-the Art Lectures

1980 Plenary presentation. California Society of Pathologists 33rd Annual Convention, San Francisco, CA
1982 Honor lecture. Annual Meeting of the Italian Diabetes Association, Bari, Italy
1988 Plenary presentation. Schepens International Society, Paris, France
1989 Plenary presentation. 21st Meeting of the Diabetic Pregnancy Study Group, Uppsala, Sweden
Plenary presentation. Schepens International Society, Rome, Italy
1991 Plenary presentation. State-of-the-Art Symposium at Annual Meeting of the European Association for the Study of Diabetes, Dublin, Ireland
1992 Plenary presentation. Vitreo-Retinal Symposium VIII, Association pour la Recherche Sur les Maladies de la Rétine, Paris, France
1994 State-of-the-Art lecture at Symposium on Diabetes and Endothelial Cell Dysfunction, Kyoto, Japan
1995 International Guest Lecturer at the Annual Meeting of the European Diabetic Nephropathy Study Group, Heidelberg, Germany
1998 Plenary presentation. 8th Annual University Diabetes Symposium, Southern Illinois University School of Medicine, Springfield, IL
Plenary presentation. Scandinavian Society for the Study of Diabetes, HelsingØr, Denmark.
Plenary presentation. European Society for Microcirculation, Paris, France
2000 Plenary Lecture. The Jubilee Symposium on Diabetes, University of Rome and National Research Council, Rome, Italy
2001 Keynote Speaker. Regional Congress of the Italian Diabetes Association; Genova, Italy
Keynote Speaker. Symposium of the Regional Assembly of the Italian Diabetes Association, Turin, Italy
2003 Plenary Lecture. 18th International Diabetes Federation Congress, Paris, France
Honor Lecture. 700th Anniversary of The University of Rome "La Sapienza" Rome, Italy
2004 Honor Lecture. Symposium "Cellular and Molecular Biology in the Study of Diabetic Microangiopathy" Istituto Superiore di Sanita, Rome, Italy
2006 Keynote Speaker. Symposium "Prevention of Diabetic Complications". Istituto Superiore di Sanita, Rome,

Italy.

2007 Keynote Lecture, 17th Meeting of the European Association for the Study of Diabetes Eye Complications Study Group, Rome, Italy
Plenary Lecture, XIII InterAssociation Congress AMD-SID (Association of Diabetes Physicians and Italian Society of Diabetes), Milan, Italy
Honor Lecture, Annual Scientific Meeting of the Italian Society of Diabetes, Olbia, Sardinia, Italy
Keynote Speaker, 7th Forum Diabetes Youth, Italian Society of Pediatric Diabetes and Novo Nordisk, Genova, Italy

2009 Honor Lecture, Joint Meeting of the Association Young Diabetic Patients and University of Milano, Milan, Italy

Invited Lectures, Seminars, Grand Rounds (selected list)

1980 Seminar. University of California San Francisco Department of Laboratory Medicine, San Francisco, CA
1984 Lecture. Workshop of the 31st Postgraduate Course of the American Diabetes Association, Los Angeles, CA
1985 Lecture. 4th European Symposium on Metabolism, Padova, Italy
1986 Seminar. Medical Societies of Imperia and Genova, Italy
Seminar. Eye Research Institute, Boston, MA
1988 Lecture. Istituto Scientifico di Medicina Interna, University of Genova, Italy
Lecture. Symposium on Cellular Aspects of the Etiology of Diabetic Vascular Complications, 13th International Diabetes Federation Congress, Sidney, Australia
Lecture. Symposium on Endothelial Cell Function in Diabetic Microangiopathy, Melbourne, Australia
1989 Seminar. The Rockefeller University, New York, NY
Lecture. International Symposium on Circulating Regulatory Factors and Neuroendocrine Function, Bratislava, Czechoslovakia
Lecture. 15th World Congress of the International Union of Angiology, Rome, Italy
1990 Lecture. International Symposium on Diabetic Complications: Epidemiology and Pathogenetic Mechanisms, Lisbon, Portugal
Endocrine Grand Rounds, Case Western Reserve University School of Medicine, Cleveland, OH
Pathology Grand Rounds, Case Western Reserve University School of Medicine, Cleveland, OH
Lecture. VI Vitreo-Retinal Symposium, Fontainebleau, France
Lecture. 25th International Research Symposium of the American Diabetes Association, Woods Hole, MA
Endocrine Grand Rounds, Rhode Island Hospital, Brown University, Providence, RI
1991 Visiting Scholar, Vision Science Research Center, University of Alabama, Birmingham, AL
Seminar. Department of Medicine, University of Genova, Italy
Lecture. European Association for the Study of Diabetes - Study group on Diabetic Eye Disease, Hammersmith Hospital, London, England
Lecture. University of Pennsylvania Symposium on Diabetic Complications, Scheie Eye Institute, University of Pennsylvania Philadelphia, PA
Lecture. Seminars on Diabetes, University of Minnesota Diabetes Center, Minneapolis, MN
1992 Seminar. Department of Medicine, University of Genova, Italy
Lecture. Symposium on Age-Related Macular Degeneration and Diabetic Retinopathy. Palm Beach, FL
1993 Lecture. The First International Workshop "Diabetic Retinopathy: What Do We Really Know?" The Milton S. Hershey Medical Center, Penn State College of Medicine, Hershey, PA
Visiting Professor. Department of Internal Medicine, University of Vienna, Austria
1994 Seminar. Shiga University of Medical Science, Otsu, Japan
Lecture. Workshop on Diabetic Angiopathy of the European Society for Clinical Investigation, Toledo, Spain
1995 Seminar. Ospedale San Raffaele University of Milano, Italy
1996 Seminar. Department of Medicine, University of Genova, Italy
1997 Lecture. International Diabetes Conference on Molecular and Cell Biology of Type II Diabetes and its Complications, Turin, Italy
Lecture. Retina 2000 Conference of the Schepens International Society, Boston, MA
Lecture. 16th International Diabetes Federation Congress, Helsinki, Finland
Lecture. Oxford Workshop on Diabetic Retinopathy, Oxford, England
Lecture. Symposium on "Acarbose - Challenges and Opportunities," Orlando, FL
1998 Visiting Professor, Center for Clinical Neuroscience and Ophthalmology, Michigan State University
1999 Lecture. Children's Hospital Medical Center, Cincinnati, OHLecture. Department of Nutrition, Harvard School of Public Health, Boston, MA
Lecture. Meeting on Endothelial Cell Function in Diabetes Mellitus, Wellcome Trust, Genome Campus,

Hinxton Hall, England
Lecture. VIII Diabetes Meeting of the Medical Academy of Pistoia; Pistoia, Italy

2000 Lecture. Seminars in Vascular Biology, Children's Hospital, Harvard Medical School, Boston, MA
Lecture. Department of Medicine, Massachusetts General Hospital, Boston, MA
Lecture. Workshop on Genetics of Diabetic Retinopathy, National Eye Institute, Bethesda, MD

2001 Lecture. University of Padova; Padova, Italy.
Lecture. Special Interest Group meeting; annual meeting of the Association for Research in Vision and Ophthalmology; Ft. Lauderdale, FL
Lecture. Endocrine Unit, Massachusetts General Hospital, Boston, MA
Lecture. Mount Sinai Diabetes Meeting, Mount Sinai School of Medicine, New York, NY

2002 Lecture. Vascular Biology Institute, University of Miami School of Medicine, Miami, FL

2003 Lecture. DCCT/EDIC 20th Anniversary Symposium; NIH Campus, Bethesda, MD
Seminar. Pediatric Endocrinology, Massachusetts General Hospital, Boston, MA
Seminar. Pfizer Central Research, Groton, CT

2004 Lecture. International Polyol Pathway Conference, Kona, Hawaii
Lecture. Istituto Giannina Gaslini for Pediatric Diabetes, University of Genova; Genova, Italy

2005 Seminar. Bausch & Lomb, Rochester, NY

2006 Seminar. Kresge Eye Institute, Detroit, MI
Seminar. Department of Ophthalmology, Istituto Scientifico-Ospedale San Raffaele, Milano, Italy
Lecture, HMS Department of Ophthalmology Annual Meeting, Boston, MA

2007 Invited presentation, NIDDK Workshop "Advances toward measuring diabetic retinopathy and neuropathy", Baltimore, MD
Seminar, Institute for Neurosciences, Comitato Nazionale delle Ricerche (CNR), Pisa, Italy
Seminar, Departments of Pharmacology and Ophthalmology University of Florida, Gainesville, FL

2008 Lecture, 22nd National Meeting of the Italian Society of Diabetes, Torino, Italy
Lecture, Postgraduate Course of the International School of Pediatric Sciences Istituto Giannina Gaslini, University of Genova, Genova, Italy

2009 Presentation at XIV Workshop in Pediatric Endocrinology and Metabolism, Pediatric Department Scientific Institute San Raffaele, Milan, Italy

2) Original articles

1. Gerich JE, Lorenzi M, Schneider V, Karam JH, Rivier J, Guillemin R, Forsham PH. Effects of somatostatin on plasma glucose and glucagon levels in human diabetes mellitus: pathophysiologic and therapeutic implications. N Engl J Med. 1974;291:544-547.
2. Gerich JE, Lorenzi M, Schneider V, Forsham PH. Effect of somatostatin on plasma glucose and insulin responses to glucagon and tolbutamide in man. J Clin Endocrinol Metab. 1974;39:1057-1060.
3. Gerich JE, Lorenzi M, Schneider V, Kwan CW, Karam JH, Guillemin R, Forsham PH. Inhibition of pancreatic glucagon responses to arginine by somatostatin in normal man and in insulin-dependent diabetics. Diabetes. 1974;23:876-880.
4. Gerich JE, Lorenzi M, Hane S, Gustafson G, Guillemin R, Forsham PH. Evidence for a physiologic role of pancreatic glucagon in human glucose homeostasis: studies with somatostatin. Metabolism. 1975;24:175-182.
5. Gerich JE, Lorenzi M, Karam JH, Schneider V, Forsham PH. Abnormal pancreatic glucagon secretion and postprandial hyperglycemia in diabetes mellitus. JAMA. 1975;234:159-165.
6. Gerich JE, Tsalikian E, Lorenzi M, Karam JH, Bier DM. Plasma glucagon and alanine responses to acute insulin deficiency in man. J Clin Endocrinol Metab. 1975;40:526-529.
7. Gerich JE, Lorenzi M, Bier DM, Schneider V, Tsalikian E, Karam JH, Forsham PH. Prevention of human diabetic ketoacidosis by somatostatin: evidence for an essential role of glucagon. N Engl J Med. 1975;292:985-989.
8. Lorenzi M, Gerich JE, Karam JH, Forsham PH. Failure of somatostatin to inhibit tolbutamide-induced insulin secretion in patients with insulinomas: a possible diagnostic tool. J Clin Endocrinol Metab. 1975;40:1121-1124.
9. Tyrrell JB, Lorenzi M, Gerich JE, Forsham PH. Inhibition by somatostatin of ACTH secretion in Nelson's syndrome. J Clin Endocrinol Metab. 1975;40:1125-1127.
10. Mielke CH Jr, Gerich JE, Lorenzi M, Tsalikian E, Rodvien R, Forsham PH. The effect of somatostatin on coagulation and platelet function in man. N Engl J Med. 1975;293:480-483.
11. Gerich JE, Tsalikian E, Lorenzi M, Schneider V, Bohannon NV, Gustafson G, Karam JH. Normalization of fasting hyperglucagonemia and excessive glucagon responses to intravenous arginine in human diabetes mellitus by prolonged infusion of insulin. J Clin Endocrinol Metab. 1975;41:1178-1180.
12. Gerich JE, Schneider VS, Lorenzi M, Tsalikian E, Karam JH, Bier DM, Forsham PH. Role of glucagon in human diabetic ketoacidosis: studies using somatostatin. Clin Endocrinol. 1976;5(Suppl):299s-305s.

13. Gerich JE, Lorenzi M, Tsalikian E, Karam JH. Studies on the mechanism of epinephrine-induced hyperglycemia in man: evidence for participation of pancreatic glucagon secretion. Diabetes. 1976;25:65-71.
14. Karam JH, Rosenthal M, O'Donnell JJ, Tsalikian E, Lorenzi M, Gerich JE, Siperstein MD, Forsham PH. Discordance of diabetic microangiopathy in identical twins. Diabetes. 1976; 25:24-28.
15. Gerich JE, Lorenzi M, Bier DM, Tsalikian E, Schneider V, Karam JH, Forsham PH. Effects of physiologic levels of glucagon and growth hormone on human carbohydrate and lipid metabolism: studies involving administration of exogenous hormone during suppression of endogenous hormone secretion with somatostatin. J Clin Invest. 1976;57:875-884.
16. Gerich JE, Langlois M, Noacco C, Lorenzi M, Karam JH, Forsham PH, Gustafson G. Comparison of the suppressive effects of elevated plasma glucose and free fatty acid levels on glucagon secretion in normal and insulin-dependent diabetic subjects: evidence for selective alpha-cell insensitivity to glucose in diabetes mellitus. J Clin Invest. 1976;58:320- 325.
17. Gerich JE, Lorenzi M, Tsalikian E, Bohannon NV, Schneider V, Karam JH, Forsham PH. Effects of acute insulin withdrawal and administration on plasma glucagon responses to intravenous arginine in insulin-dependent diabetic subjects. Diabetes. 1976;25:955-960.
18. Gerich JE, Karam JH, Lorenzi M. Diabetes without glucagon. Lancet. 1976;1:855.
19. Deftos LJ, Lorenzi M, Bohannon N, Tsalifian E, Schneider V, Gerich JE. Somatostatin does not suppress plasma parathyroid hormone. J Clin Endocrinol Metab. 1976;43:205-207.
20. Tsalikian E, Dunphy TW, Bohannon NV, Lorenzi M, Gerich JE, Forsham PH, Kane JP, Karam JH. The effect of chronic oral antidiabetic therapy on insulin and glucagon responses to a meal. Diabetes. 1977; 26:314-321.
21. Tyrrell JB, Wiener-Kronish J, Lorenzi M, Brooks RM, Forsham PH. Cushings disease: growth hormone response to hypoglycemia after correction of hypercortisolism. J Clin Endocrinol Metab. 1977; 44:218-221.
22. Bohannon NV, Karam JH, Lorenzi M, Gerich JE, Matin SB, Forsham PH. Plasma glucagon suppression by phenformin in man. Diabetologia. 1977; 13:503-508.
23. Goldberg ML, Bohannon NV, Brooks RM, Tsalikian E, Lorenzi M, Forsham PH. Plasma cyclic nucleotide levels in juvenile-onset diabetes. Diabetes. 1977; 26:936-943.
24. Lorenzi M, Tsalikian E, Bohannon NV, Gerich JE, Karam JH, Forsham PH. Differential effects of L-dopa and apomorphine on glucagon secretion in man: evidence against central dopaminergic stimulation of glucagon. J Clin Endocrinol Metab. 1977; 45:1154-1158.
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28. Lorenzi M, Karam JH, Tsalikian E, Bohannon NV, Gerich JE, Forsham PH. Dopamine during □- or □-adrenergic blockade in man: hormonal, metabolic, and cardiovascular effects. J Clin Invest. 1979; 63:310-317.
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31. Lorenzi M, Karam JH, McIlroy MB, Forsham PH. Increased growth hormone response to dopamine infusion in insulin-dependent diabetic subjects: indication of possible blood-brain barrier abnormality. J Clin Invest. 1980; 65:146-153.
32. Schmitt JK, Davis JL, Lorenzi M, Benet LZ, Burns A, Karam JH. Inhibition by indomethacin of the glycemic response to arginine in man. Proc Soc Exp Biol Med. 1980; 163:237-239.
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35. Lorenzi M, Goldbaum MH, Spencer EM, Cheney C. Improved diabetic control and retinopathy. N Engl J Med. 1983; 308:1600.
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41. Lorenzi M, Karam JH. Human insulin in the treatment of insulin allergy. West J Med. 1985; 143:387-388.
42. Lorenzi M, Healy DP, Hawkins R, Printz JM, Printz MP. Studies on the permeability of the blood-brain barrier in experimental diabetes. Diabetologia. 1986; 29:58-62.
43. Lorenzi M, Montisano DF, Toledo S, Barrieux A. High glucose induces DNA damage in cultured human endothelial cells. J Clin Invest. 1986; 77:322-325.
44. Lorenzi M, Toledo S. Myoinositol enhances proliferation of cultured human endothelial cells but fails to correct the delay induced by high glucose. Metabolism. 1986; 35:824-829.
45. Cagliero E, Lorenzi M. The corticotropin-releasing factor test in the diagnosis of ectopic ACTH secretion. West J Med. 1987; 146:614-615.
46. Lorenzi M, Montisano DF, Toledo S, Wong HC. Increased single strand breaks in DNA of lymphocytes from diabetic subjects. J Clin Invest. 1987; 79:653-656.
47. Lorenzi M, Toledo S, Boss G, Lane M, Montisano D. The polyol pathway and glucose-6-phosphate in human endothelial cells cultured in high glucose concentrations. Diabetologia. 1987; 30:222-227.
48. Lorenzi M, Nordberg JA, Toledo S. High glucose prolongs cell cycle traversal of human endothelial cells. Diabetes. 1987; 36:1261-1267.
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50. Diabetes Epidemiology Research International Group. Geographic patterns of childhood insulin-dependent diabetes mellitus. Diabetes. 1988; 37:1113-1119.
51. Cagliero E, Maiello M, Boeri D, Roy S, Lorenzi M. Increased expression of basement membrane components in human endothelial cells cultured in high glucose. J Clin Invest. 1988; 82:735-738.
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55. Cagliero E, Grant MB, Lorenzi M. Measurement of gene expression in human retinal microvessels by solution hybridization. Invest Ophthalmol Vis Sci. 1991; 32:1439-1445.
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60. Roy S, Maiello M, Lorenzi M. Increased expression of basement membrane collagen in human diabetic retinopathy. J Clin Invest. 1994; 93:438-442.
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63. Cagliero E, Roth T, Taylor AW, Lorenzi M. The effects of high glucose on human endothelial cell growth and gene expression are not mediated by Transforming Growth Factor-□. Lab Invest. 1995; 73:667-673.
64. Roy S, Cagliero E, Lorenzi M. Fibronectin overexpression in retinal microvessels of patients with diabetes. Invest Ophthalmol Vis Sci. 1996; 37:258-266.
65. Roy S, Lorenzi M. Early biosynthetic changes in the diabetic-like retinopathy of galactose-fed rats. Diabetologia. 1996; 39:735-738.
66. Mizutani M, Kern TS, Lorenzi M. Accelerated death of retinal microvascular cells in human and experimental diabetic retinopathy. J Clin Invest. 1996; 97:2883-2890.

67. Baumgartner-Parzer S, Wagner O, Waldhäusl W, Roth T, Lorenzi M. Failure of high ambient glucose to affect endothelin-1 synthesis or release by cultured human endothelial cells. Horm Metab Res. 1996; 28:610-612.
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69. Lopes de Faria JB, Zoukhri D, Lorenzi M. Mesangial cell abnormalities in spontaneously hypertensive rats before the onset of hypertension. Kidney Int. 1997; 52:387-392.
70. Mizutani M, Gerhardinger C, Lorenzi M. Müller cell changes in human diabetic retinopathy. Diabetes 1998; 47:445-449.
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73. Kern TS, Tang J, Mizutani M, Kowluru R, Nagaraj R, Romeo G, Podestà F, Lorenzi M. Response of capillary cell death to aminoguanidine predicts the development of retinopathy: Comparison of diabetes and galactosemia. Invest Ophthalmol Vis Sci. 2000; 41:3972-3978.
74. Gerhardinger C, McClure KD, Romeo G, Podestà F, Lorenzi M. IGF-I mRNA and signaling in the diabetic retina. Diabetes 2001; 50:175-183.
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77. Zhang J, Gerhardinger C, Lorenzi M. Early complement activation and decreased levels of glycosylphosphatidylinositol-anchored complement inhibitors in human and experimental diabetic retinopathy. Diabetes 2002; 51:3499-3504.
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79. Dagher Z, Park YS, Asnaghi V, Hoehn T, Gerhardinger C, Lorenzi M: Studies of rat and human retinas predict a role for the polyol pathway in human diabetic retinopathy. Diabetes 2004; 53:2404-2411.
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3) Proceedings of meetings

1. Lorenzi M, Toledo S, Boss G. On the mechanisms of the ill effects of high glucose on vascular endothelium. In: Crepaldi G, Tiengo A, Baggio G, eds. Diabetes, Obesity and Hyperlipidemias - III. Amsterdam: Excerpta Medica, 1985: 385-389.
2. Lorenzi M, Cagliero E, Maiello M, Boeri D. Diabetic hyperglycemia as a risk factor for atherogenesis: Lessons from an in vitro model and therapeutic implications. In: Strano A, Novo S, eds. Advances in Vascular Pathology 1989 - Vol 2. Amsterdam: Excerpta Medica, 1989:1381-1388.
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4) Reviews and book chapters

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5) Abstracts (of work not yet published)

1. Dagher Z, Hoehn T, Romeo G, Lorenzi M. The absence of Bax prevents the sight-threatening capillary loss of diabetic retinopathy. Presented at the American Diabetes Association 65th Annual Meeting, San Diego, CA, June 10-14, 2005; Diabetes 2005; 54 (Suppl 1):A221.
2. Feke GT, Kolodjaschna J, Pitler L, McMeel JW, Lorenzi M. Abnormal retinal vascular reactivity in response to posture change in well-controlled type 1 diabetic patients with no retinopathy. Presented (oral) at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Ft. Lauderdale, FL, April 27- May 1, 2008; Invest Ophthalmol Vis Sci 2008; 49: E-Abstract 3263.
3. Lorenzi M, Feke GT, Berisha F, Kolodjaschna J, Pitler L. Defective retinal vascular reactivity to a change in blood pressure as a risk marker for diabetic retinopathy. Presented (oral) at the 18th Meeting of the European Association for the Study of Diabetes Eye Complications Study Group (EASDec), Amsterdam, The Netherlands, May 30-June 1, 2008; Eur J Ophthalmol 2008; 18:491.

4. Tremolada G, Lattanzio R, Pierro L, Maestranzi G, Lorenzi M. Detection of early stages of Diabetic Macular Edema. Presented at the 18th Meeting of the European Association for the Study of Diabetes Eye Complications Study Group (EASDec), Amsterdam, The Netherlands, May 30-June 1, 2008; Eur J Ophthalmol 2008; 18:494.
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5. I work at the Schepens Eye Research Institute, Harvard Medical School (20 Staniford St. Boston MA 02114) as Professor of Ophthalmology. I am familiar with diabetic retinopathy and diabetic macular edema and I declare the following opinions and facts as an expert.

1) I believe that there are clear differences between diabetic retinopathy and diabetic macular edema. The end stage of diabetic retinopathy is blindness (loss of light perception), and that of diabetic macular edema (DME) is a severe blurred vision or doubling of the visual angle. DME is not simply a symptom of retinopathy. While diabetic retinopathy is necessary for DME to develop, it is not sufficient; and the development of DME appears to require mechanisms additional to those involved in the development of retinopathy. DME can be viewed as a "complication" of retinopathy. Diabetic retinopathy and DME are considered to be different conditions. This is demonstrated by several observations:

(a) Only a fraction of patients with diabetic retinopathy develop DME, even after many years of retinopathy. In the landmark study on the epidemiology of DME --the Wisconsin Epidemiologic Study of Diabetic Retinopathy XV --The Long-term Incidence of Macular Edema (Klein R et al, *Ophthalmology* 1995; 102:7-16), Table 3 shows that among patients with varying degrees of retinopathy only a fraction developed DME after 10 years, even when they had already severe retinopathy at the initial evaluation.

(b) Among the patients who develop DME, more have type 2 diabetes (diabetes beginning at an older age) than type 1 diabetes (insulin-dependent diabetes mostly developing at young age). This is noted in the epidemiological study by Klein et al cited above, and confirmed in a completely different population of diabetic patients evaluated at a prestigious retinal referral center (see Lopes de Faria JM et al, *Acta Ophthalmol Scand* 1999; 77:170-175). In contrast, diabetic retinopathy is more likely to affect patients with type 1 diabetes than type 2 diabetes as reported by Klein (Klein R et al, *Ophthalmology.* 1998;105:1801-1815.) and Mohamed Q (Mohamed Q et al, *JAMA* 2007, 298:902-916).

(c) There are treatment modalities specific to DME that do not address or modify the

course of diabetic retinopathy. The treatments range from focal laser to intravitreal corticosteroids as described in detail in the review by Mohamed Q et al in *JAMA* 2007, 298:902-916; the treatment of DME is described specifically on pages 911-913, and summarized on page 913. None of these treatments addresses diabetic retinopathy in general. It can be appreciated from this reference and many other articles written on the topic of DME treatment, that the current treatment of DME is only seldom curative. In many patients, DME becomes a chronic condition approached with several types of treatment without definitive success. The current treatment modalities are not sufficient to completely prevent or treat DME. Diffuse macular edema is considered to be especially difficult to manage.

2) The use of ARIs as described in the Mylari patent (US 6,426,341) – for the treatment of diabetic complications, such as diabetic retinopathy, diabetic nephropathy, etc – has not found its way into clinical medicine and has not become practice. The reasons are several, one being the fact that no clinical trial conducted to date has proven clear efficacy of the ARIs for the above indications. On this basis, one of ordinary skill in the art would not expect that ARI be effective in the prevention or treatment of early macular edema.

SNK-860 inhibits macular edema formation in the monkey model, shown in efficacy pharmacological test example 3 on page13. Among patients with diabetic maculopathy, an effect on the thickness of the macula lutea was confirmed, as shown in efficacy pharmacological test example 4 on page15. SNK-860 had a visual acuity-improving action important in the therapy of maculopathy. On account of the above considerations, these results are considered to be surprising and not to be obvious to one of ordinary skill in the art.

6. I confirm that I am being compensated by the assignee of the present application for the time spent in making this Declaration.

7. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Date: June 10, 2009

Mara Lorenzi

Name: Mara Lorenzi

Title: Professor of Ophthalmology
Harvard Medical School
Schepens Eye Research Institute